Rejections Under 35 U.S.C. §103(a)

The Office Action maintained the rejection of Claims 7, 8 and 16-21 (AW), *Lucklow et al., Matsuura et al.* and *Krishna et al.* The Office Action stated that it would have been obvious at the time the claimed invention was made to express the gG-2 protein of *Lee et al.* (AA1) and the gG-1 protein of Lee *et al.* (AW) in the baculovirus expression system of *Lucklow et al., Matsuura et al.* or *Krishna et al.* with the expected benefit of obtaining gG-1 and gG-2 proteins suitable for use in diagnostic immunoassays and/or kits with the further expectation of successively detecting HSV type-specific antibodies in serum samples as taught by *Lee et al.* (AA1) and *Lee et al.* (AW). Therefore, the Office Action contends that the combined prior art renders the claimed invention obvious. Applicants respectfully traverse this rejection.

The Office Action and the Interview Summary record objected to Applicants' previous arguments because no evidence has been presented to distinguish the presently claimed recombinant HSV antigen from other recombinant HSV antigens, thus demonstrating unexpected and surprising results. In response, Applicants provide herewith the Declaration under 37 C.F.R. §1.132 of Philip E. Pellett, co-inventor of the above-identified application.

The Declaration states that Dr. Pellett and his colleagues designed several experiments to demonstrate differences between herpesvirus glycoprotein gG-1 produced using the novel recombinant baculovirus vector AcDSMgG-1 and the herpesvirus glycoprotein gG-1 produced using the baculovirus vector Ac373'gG-1. The results of these experiments are best shown in the data published in the scientific article entitled "Expression of HSV-1 and HSV-2 Glycoprotein G in Insect Cells by Using a Novel Baculovirus Expression Vector", authored by Demetrio Sanchez-Martinez in *Virology* 182: 229-238 (1991), a reprint of which is attached hereto as Exhibit A.

The novel baculovirus vector AcDSMgG-1 was constructed by effectively removing a nucleotide region from the pAcDSM transfer vector (between the *Pst*I and *Hind*III restriction sites) and inserting in its place a synthetic oligomer followed by the engineered gene as shown in Figure 1, Panel B of Exhibit A. As shown in Figure 1, Panel C of Exhibit A (page 231), in the novel AcDSMgG-1 vector, the nucleotide sequence 5' to the translation initiation codon is identical to and aligns with that of wild type AcNPV (polyhedrin), whereas the Ac373'gG-1 vector includes 21 extraneous nucleotides. By constructing a vector in this way, the novel baculovirus

transfer vector pAcDSM joins the herpes simplex virus type 1 glycoprotein gene (or type 2 glycoprotein gene) precisely at the translation initiation codon of the polyhedrin gene.

It was unexpectedly discovered that the novel baculovirus vector AcDSMgG-1 not only produces more glycoprotein than the Ac373'gG-1 vector, indicating a **higher level of expression**, but the novel baculovirus vector produces proteins having different electrophoretic band patterns than produced from the Ac373'gG-1 vector, indicating that the recombinant proteins are **structurally different**. These observations are explained on page 233, left column, first full paragraph, of Exhibit A, which is reproduced as follows:

> Expression of the recombinant gG-1 is differed in two respects. (i) The intensity of the reaction with both antibodies was higher in extracts of cells infected with AcDSMgG-1 than with Ac373'gG-1 (Fig. 2A). (ii) In extracts of Sf9 cells infected with AcDSMgG-1, 42K reacted more than 37K. In extracts of Sf9 cells infected with Ac373'gG-1, the opposite was true, with 42K being very faint.

These results are best shown in Figure 2 of Exhibit A (page 233). Panel A of Figure 2 shows photographs of two electrophoretic gels. The gel on the left was reacted with antibodies from human serum identified as HSV-1 positive and HSV-2 negative. The gel on the right was reacted with a monoclonal antibody specific for gG-1 (H1379). The left two lanes of each gel represent SDS-PAGE separations of the glycoprotein products of vector Ac373'gG-1 and novel vector AcDSMgG-1, respectively, with molecular mass standards shown on the left side of each gel. The remaining two lanes of each gel are controls.

In both the human serum reactive and the monoclonal antibody reactive gels, the glycoprotein product of vector Ac373'gG-1 shows a high intensity band at approximately 37 kDa and a low intensity band at 42 kDa. In contrast, the glycoprotein product produced by the novel vector AcDSMgG-1 shows a very high intensity band at approximately 42 kDa and a lower intensity band at approximately 37 kDa. It is interesting to note that the 37 kDa bands for both the Ac373'gG-1 and AcDSMgG-1 have similar intensities, demonstrating that the differences in intensities for the 42 kDa band are due to physical differences in the proteins rather than the overall increase in expression by the AcDSMgG-1 vector.

Panel B of Figure 2 is a photograph of a slot-blot analysis of serial dilutions of gG-1 expressed in Sf9 cells by the recombinant vectors Ac373'gG-1 and AcDSMgG-1. The dilution factor is shown to the right. Cell extracts similar to those used in Panel A were four-fold serially diluted in phosphate-buffered saline, bound to a nitrocellulose membrane using a slot-blot apparatus, and reacted with the gG-1-specific monoclonal antibody used in Panel A (H1379). As can be clearly seen in the slot-blot, immunoreactive protein diluted by a factor of 64 was detected in the cell extracts produced by the novel baculovirus vector AcDSMgG-1, whereas immunoreactive protein produced by the Ac373'gG-1 vector was only detectable up to a dilution factor of 16. Therefore, the level of expression of gG-1 by the baculovirus vector AcDSMgG-1 was approximately four-fold greater than the level of gG-1 expression by the Ac373'gG-1 vector. It is well known by those skilled in the art that a recombinant protein produced at a higher level of expression provides a purer product.

In conclusion, the data described above clearly demonstrate that the glycoprotein gG-1 produced from the novel baculovirus vector AcDSMgG-1 is physically different from the gG-1 glycoprotein produced by the baculovirus vector Ac373'gG-1. In addition, the level of expression of gG-1 by the novel baculovirus vector AcDSMgG-1 is significantly higher, thereby resulting in a purer product. In view of the present Declaration, Applicants request removal of the remaining rejection and allowance of the claims.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 10-1215.

The foregoing is submitted as a full and complete Response to the Office Action mailed February 3, 1998. This Response places all claims in the present application in condition for allowance, and such action is courteously solicited. The Examiner is invited and encouraged to contact the undersigned attorney of record if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

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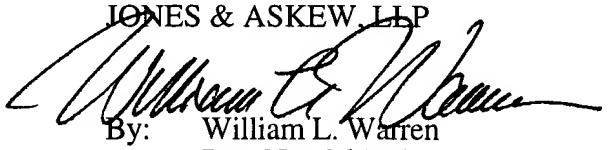

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